PEC UPDATE

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ISSUE HIGHLIGHTS

Management of Asthma

The initial Tri-Service Formulary (TSF) was approved in November 1993. Since this time the PEC has completed five major disease state reviews resulting in changes to the TSF. The management of asthma is the sixth major disease state analysis conducted by the PEC resulting in changes to the TSF. This PEC Update contains TSF changes, cost-effectiveness model, treatment guidelines, preferred drug lists, and drug usage evaluation criteria for the treatment of asthma.

Executive Summary

The Department of Defense (DOD) spends more than $19 million per year on the drug treatment of asthma. However, a recent study demonstrated that many DOD patients are not receiving appropriate treatment and are not well versed in home management of asthma.

This guideline is designed as a tool for the primary care provider treating patients with mild through moderate disease. Patients with severe disease frequently require individualized case management coordinated by an asthma specialist, and are beyond the scope of this guideline.

Airway inflammation has recently been recognized as an important factor in the pathogenesis of airway hyper-responsiveness and reversible airway obstruction in defining asthma. Increasing prevalence and morbidity and mortality of asthma require greater awareness of the need to successfully treat underlying inflammation in accordance with existing guidelines. Recent DOD studies have recognized the need for improved case management and increased use of antiinflammatory agents. The development of inhaled steroids has been the greatest advance in asthma therapy in recent years, and steroid inhalation should be first-line therapy for chronic asthma. **An inhaled corticosteroid is the appropriate first treatment for patients who need inhalation therapy with beta$_2$-adrenergic-receptor agonists more than once daily**, as recommended by national and international guidelines.

The goal of management is to achieve control of asthma, which is defined as:

- Minimal (ideally no) chronic symptoms, including nocturnal symptoms
- Minimal (infrequent) exacerbations
- No emergency visits
- Minimal (ideally no) need for *as needed* beta$_2$-agonist therapy
- No limitations on activities, including exercise

- Peak expiratory flow (PEF) circadian variation of less than 20 percent
- (Near) normal PEF
- Minimal (or no) adverse effects from medication

"Controller" and " reliever" medications are discussed in detail, as well as currently recognized international guidelines for therapy. Controllers are chronic medications taken daily that are useful for getting and keeping persistent asthma under control. Antiinflam-matory agents and long-acting bronchodilators are included in this category. **The inhaled corticosteroid antiinflammatory agents are now the most effective controller medications.**

Relievers include short-acting bronchodilating medications that act quickly to relieve broncho-constriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. They have been labeled as quick relief medicine or rescue medicine.

A stepwise approach to therapy recommends that the number (type) and frequency of medications are increased with increasing asthma severity (step up). The aim is to accomplish the goals of therapy with the least possible medication. Once control is sustained for about 3 months, a reduction in therapy, a stepdown, can be carefully considered.

- Step 1: Intermittent Asthma
- Step 2: Mild Persistent Asthma
- Step 3: Moderate Persistent Asthma
- Step 4: Severe Persistent Asthma

Step therapy is presented, and cost-effectiveness of the various therapeutic choices available for Steps 2 and 3 are evaluated from the perspective of the DOD as the payer of health care benefits.

Initiation of appropriate therapy at the earliest possible signs of deteriorating control of asthma is important in the successful management of asthma exacerbations. When patients are able to begin treatment at home, they not only avoid delays in treatment but also add to their sense of control over their asthma. The degree of care provided in the home depends on the health care professional's and patient's (or parents') experience and the availability of medications and emergency care. Ideally, **all patients should have an action plan that outlines how and when to :**

- Recognize signs of deterioration
- Start treatment
- Get medical care

Referral to an asthma specialist should be considered for:

(a) Patients in whom the diagnosis is in doubt.
(b) Patients with possible occupational asthma.
(c) Patients with asthma whose management is complex:
    - those who have recently been discharged from the hospital.
    - those with catastrophic suddenly severe (brittle) asthma.
    - those with continuing symptoms despite high doses of inhaled steroids (800-1,200 mcg/day).
    - those being considered for long term treatment with nebulized bronchodilators.
    - pregnant women with worsening asthma.
    - patients whose asthma is interfering with their lifestyle.

Preventive case management is recognized as a key factor in quality improvement. Resulting cost savings and examples of DOD programs are provided in Appendix A. In addition, sample drug use evaluation criteria are included in Appendix B for local adaptation and use.

Methodology:

A mathematical cost-effectiveness model was developed from the perspective of the Department of Defense as the payer of healthcare benefits.

Step 2 therapy for both adult and pediatric patients was modeled, using the percent of symptom free days as the outcome measure. The outcome measure was decremented by compliance with the dosing regimen and the dropout rate for the medication to determine the overall effectiveness of the treatment regimen. The medications included in the model were the inhaled corticosteroids, cromolyn, nedocromil, and theophylline. Direct care costs, including physician visits, laboratory study costs, and drug acquisition costs were included in the model, as well as the costs of treatment failure and theophylline toxicity. Opportunity costs (lost productivity) were not included as the prevalence of asthma requiring Step 2 therapy in the active-duty population is assumed to be very low.

Step 3 therapy was modeled as therapy independent of the Step 2 therapy used. It was assumed that maximal Step 2 therapy was used prior to adding Step 3 therapy. In addition, the outcome measure used for Step 3 therapy was lack of nocturnal awakenings which was decremented in the same manner as above to determine the overall effectiveness. The medications included in this model were long-acting beta-agonists (oral and inhaled) and

theophylline. Since the majority of the direct care costs were included the Step 2 therapy model, they were not included a second time in the Step 3 model. Direct care costs that were included were the additional costs of monitoring theophylline therapy.

Step 4 therapy was not modeled, as it is patient-specific and requires referral to an asthma specialist.

Spacers were evaluated by a consultant panel of physicians by ranking the spacers based on a list of 10 attributes. Based on this expert opinion, the spacer that received the highest ranking on all attributes is the InspirEase®.

Because the use of short-acting inhaled $beta_2$-agonists is limited to use as needed, the selection is based on acquisition cost. The least expensive agent is albuterol.

Sensitivity Analysis:
The models were tested for robustness through the use of Monte Carlo analysis. Results of the Monte Carlo analysis showed that the model was sensitive to one variable, compliance with the dosing regimen. The model was robust to changes in the other variables and to the assumptions used in the modeling. The Monte Carlo analysis (using 1000 trials) of the variables produced slight changes in the average cost-effectiveness ratio, but no changes occurred in the relative ranking of the therapies.

Univariate analysis of the individual variables produced the same results as the Monte Carlo analysis of all the variables.

Tri-Service Formulary Selections
The Tri-Service Formulary (TSF) selections for the treatment of asthma are albuterol oral inhaler, flunisolide oral inhaler, triamcinolone acetonide oral inhaler, oral prednisone tablets, oral prednisone and prednisolone solutions, theophylline liquid, SloBid™ Gyrocaps, and InspirEase® spacer.

Tri-Service Formulary Revisions Resulting from Asthma Review

AHFS Category*		Action
12:12	***Sympathomimetic (Adrenergic) Agents***	
	Albuterol metered dose oral inhaler	Retain
	Oral terbutaline tablets 5 mg	Delete
68:04	***Adrenals***	
	Beclomethasone dipropionate metered dose oral inhaler	Delete
	Flunisolide metered dose oral inhaler	Add
	Prednisone oral solution 5 mg/5 mL	Add
	Prednisolone oral solution 15 mg/5 mL	Add
	Prednisone oral tablets 5 and 20 mg	Retain
	Triamcinolone acetonide metered dose oral inhaler	Add
86:16	***Respiratory Smooth Muscle Relaxants***	
	Theophylline liquid 80 mg/15 mL	Add
	SloBid™ Gyrocaps 50, 200, and 300 mg	Add
94:00	***Devices***	
	InspirEase® spacer	Add

*AHFS - American Hospital Formulary Service

Management of Asthma

I. Introduction

Asthma is a heterogenous disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli. It is manifested by a widespread airway narrowing that changes in severity, either spontaneously or because of therapy.[1] In 1991 the definition of asthma was revised to include the following characteristics: 1) airway inflammation, 2) airway hyper-responsiveness, and 3) reversible airway obstruction.[2,3]

Bronchial hyper-responsiveness is an exaggerated bronchoconstrictor response of the airways to a variety of nonspecific stimuli (e.g., methacholine, histamine, cold air, hypotonic or hypertonic saline, sulfur dioxide). The magnitude of hyper-responsiveness correlates with the clinical severity of asthma, and changes in reactivity are associated with changes in airway inflammation. Thus, exposure to an allergen or certain environmental pollutants can increase airway inflammation and increase airway reactivity.[4] Although it has long been recognized that fatal asthma is associated with marked inflammatory changes in the submucosa of the airways, inflammation is apparently present even in patients with very mild asthma.[4]

Epidemiologic studies of asthma have changed the way we think about this disease. Significant increases in prevalence rates, hospitalizations, and deaths due to asthma in the United States from 1965 to the present have shifted attention away from the idea of asthma as a mild, episodic disease of smooth muscle to a focus on the inflammatory components of this potentially serious disease. Asthma is much more than bronchoconstriction, and treatment must reduce inflammation and promote bronchodilation.

Clinical manifestations of asthma include episodic shortness of breath with bilateral wheezing that is usually brought on by some stimulus (Table 1).[5] Atypical manifestations of asthma, such as a chronic persistent cough without an audible wheeze, should also be kept in mind.

Skin tests with allergens represent the primary diagnostic tool in allergy[6] allowing for identification of triggers and appropriate environmental control measures. Prick tests are more commonly used and are less expensive than measurement of specific IgE in serum; however, a positive test is not conclusive for causation.

II. Asthma in the DOD Beneficiary Population

The Department of Defense (DOD) spends more than $19 million per year on the drug treatment of asthma. The distribution of asthma within DOD beneficiaries is skewed toward the pediatric age group compared with the general population because asthma or a history of asthma renders an individual unsuitable for military service. Exceptions are made for active-duty members with mild, intermittent disease for the convenience of the service.

The DOD Civilian External Peer Review Program recently released the first of a two-part study on the treatment of pediatric asthma in 11 DOD medical treatment facilities. The report showed that asthma discharge rates appear higher in the Military Health Services System than for the nation as a whole. The consultants found most of the inpatients were treated according to the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) guidelines. However, few patients were using antiinflammatory agents before admission although many patients were admitted or treated in the emergency department in the previous year. Additionally, few patients received education on home management of asthma to prevent exacerbations. The consultants concluded that there was an over reliance on the emergency department for primary care, and that morbidity and costs of hospitalization could be avoided with more consistent patient education and follow-up.[7]

NHLBI guidelines[6] include four major components: 1) pharmacologic management, 2) objective measures of lung function, 3) environmental control, and 4) patient education. Proactive case management programs that incorporate these four components can produce measurable

Table 1: Common Triggers for Asthmatic Wheezing[5]

Cigarette smoke
Aeroallergen exposure (e.g., pollen, mold, animal dander, house dust mite)
Occupational dust or fume exposure
Cosmetic products (e.g., hair spray, perfume)
Medications such as aspirin, beta blockers (including topical ophthalmic products) and nonsteroidal antiinflammatory agents
Food additives (e.g., sulfites)
Physical exercise
Emotional stress such as anger, frustration, and depression
Viral or bacterial infections of the upper respiratory tract, including sinusitis
Weather changes (i.e., sudden changes in temperature or humidity)
Air pollutants (e.g, car exhaust fumes, ozone, sulfur dioxide, nitrous oxide)
Gastroesophageal reflux

improvements in outcomes in a short period. Implementation of such a program at the National Naval Medical Center, Bethesda, MD resulted in a 33% decrease in pediatric asthma admissions in a one year period. During the same time, a 10% increase in pediatric asthma admissions was noted at the other military treatment facilities in the Washington, D.C. area where no intervention was undertaken (J. McQueston, M.D., unpublished data, 1995). Cost analysis of the program estimated up to $200,000 savings in one fiscal year providing a dramatic example of quality improvement at reduced cost.

III. Management

This treatment guideline is based on guidelines for asthma management published by the British Thoracic Society[8] and by the NHLBI.[6] Prevention of asthma involves both the prevention of the initial development of asthma (primary prevention) and the prevention of exacerbations in those who already have the condition (secondary prevention). It is assumed that primary prevention through environmental control has been maximized.

Asthma can be effectively controlled in most patients, but it cannot be cured. The major factors contributing to asthma morbidity and mortality are under-diagnosis and inappropriate treatment.

The goal of management is to achieve control of asthma, which is defined as[6]:

- Minimal (ideally no) chronic symptoms, including nocturnal symptoms
- Minimal (infrequent) exacerbations
- No emergency visits
- Minimal (ideally no) need for *as needed* beta$_2$-agonist therapy
- No limitations on activities, including exercise
- Peak expiratory flow (PEF) circadian variation of less than 20 percent
- (Near) normal PEF
- Minimal (or no) adverse effects from medication

Effective control of asthma can be accomplished through an asthma management program as depicted in Table 2.

Asthma management should be guided by the severity of the patient's condition, benefits and the risks of each treatment, and cost effectiveness of treatment. The severity of asthma is classified based on air flow limitation and its variability. Asthma can be categorized as intermittent, mild persistent, moderate persistent, and severe persistent. As the need for therapy increases, the number of medications and frequency of administration increases. The objective of a step approach is to accomplish the goals of therapy with the least possible medication. Any asthma more serious than mild, intermittent asthma is more effectively controlled by treatment to suppress and reverse the inflammation than by treatment of only acute bronchoconstriction and related symptoms.

Medications

Antiasthma drugs are classified as bronchodilator or antiinflammatory drugs.[4] A newer classification system divides them into "controllers" and "relievers" to enhance patient understanding and teaching (Table 3).[6]

Controllers are chronic medications taken daily that are useful for getting and keeping persistent asthma under control. Antiinflammatory agents and long-acting bronchodilators are included in this category. **The inhaled corticosteroid antiinflammatory agents are now the most effective controllers.**[6]

Relievers include short-acting bronchodilating medications that act quickly to relieve broncho-constriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. They have been labeled as quick relief medicine or rescue medicine.[6]

Even though the onset of action is 4 to 6 hours, systemic corticosteroids are important in the treatment of acute severe exacerbations because they prevent progression, decrease the need for emergency department visits or hospitalizations, prevent relapse, and reduce the morbidity of the illness.[6]

Table 2: Components of an Effective Asthma Management Program[6]

1. Educate patients to develop a partnership in asthma management
2. Assess and monitor asthma severity with both symptom reports and lung function measurements
3. Avoid or control asthma triggers
4. Establish individual medication plans for long-term management
5. Establish plans to manage exacerbations
6. Provide regular follow-up care

Table 3: Antiasthma Drugs

Controllers	*Relievers*
Inhaled corticosteroids	Short-acting inhaled beta$_2$-agonists
Systemic corticosteroids	Systemic corticosteroids
Sodium cromoglycate (cromolyn)	Inhaled anticholinergics
Nedocromil sodium	Short-acting theophylline
Sustained-release theophylline	Short-acting oral beta$_2$-agonists
Long-acting inhaled & oral beta$_2$-agonists	

1. Antiinflammatory Drugs

Since chronic inflammation seems central to the pathogenesis of asthma, the use of agents that suppress this process, such as corticosteroids and mediator-release inhibitors, is logical. These drugs do not have a rapid bronchodilator effect and do not provide immediate relief of symptoms, thus must be administered regularly on a long-term basis. Due to these factors, these drugs are considered prophylactic therapy.[4] Early use of these drugs in the disease process may confer longer lasting asthma control.[9]

Corticosteroids

Although corticosteroids are remarkably effective in suppressing the inflammation induced by asthma, they are still greatly under used, partly because of fears of adverse effects. The mechanism responsible for the potent antiinflammatory activity of the aerosolized drug in the lung is unknown. Glucocorticoids may decrease the number and activity of inflammatory cells, enhance the effect of beta-adrenergic drugs on cyclic AMP production, inhibit bronchoconstrictor mechanisms, or produce direct smooth muscle relaxation. Additionally glucocorticoids may inhibit transcription of genes for the cytokines implicated in asthmatic inflammation.[10,11]

The development of inhaled steroids has been the greatest advance in asthma therapy in recent years, and steroid inhalation should be first-line therapy for chronic asthma.[4] **An inhaled corticosteroid is the appropriate first treatment for patients who need inhalation therapy with beta$_2$-adrenergic-receptor agonists more than once daily**, as recommended by national and international guidelines.[6,12]

Four glucocorticoid preparations for inhalation therapy are now available in the United States: beclomethasone dipropionate, flunisolide, fluticasone propionate, and triamcinolone acetonide. No randomized, controlled clinical trials have been published comparing the efficacy or systemic toxicity of these agents. The current assumption is that they are equally effective at equivalent microgram doses, with the exception of fluticasone, which is considered to be twice as potent.[3,12-14] The number of puffs needed per day to achieve various daily doses is depicted in Table 4. The dose per puff differs among the available inhaled steroids and affects the number of puffs needed to reach the desired daily dose. Although the package insert recommends three-times-daily or four-times-daily dosing of beclomethasone and triamcinolone, twice-daily dosing has been shown to be equally effective.[15-17]

Mediator-Release Inhibitors

Cromolyn sodium, an inhaled mast cell stabilizer, inhibits the degranulation of sensitized and nonsensitized mast cells after exposure to specific antigens and prevents the release of mediators.[10] It also prevents the late response and the subsequent bronchial hyper-responsiveness that suggest inhibition of other inflammatory cells, such as macrophages or eosinophils. Cromolyn additionally prevents neurally mediated bronchoconstriction induced by sulfur dioxide and bradykinin, suggesting a possible effect on C-fiber sensory nerves in the airway. This effect has been shown experimentally and may explain why cromolyn reduces the symptoms of asthma in some patients so effectively.[4]

Nedocromil sodium is a similar inhaled antiinflammatory agent that is 4 to 10 times more potent than cromolyn. It

Table 4: Equivalent Doses of Inhaled Corticosteroids

Total daily dose	Beclomethasone 42 mcg/puff	Flunisolide 250 mcg/puff	Fluticasone* 44, 110, or 220 mcg/puff	Triamcinolone 100 mcg/puff
168 - 200 mcg	4 puffs/day	N/A	2 puffs/day of 44 mcg/puff	2 puffs/day
336 - 500 mcg	8 puffs/day	2 puffs/day	2 puffs/day of 110 mcg/puff	4 puffs/day
800 - 1000 mcg	16+ puffs/day	4 puffs/day	2 puffs/day of 220 mcg/day	8+ puffs/day

* Fluticasone is considered to be twice as potent as the other inhaled corticosteroids, thus the equipotent dose per day is approximately half of the listed total daily dose.

inhibits the release of mediators from a variety of inflammatory cell types associated with asthma, including eosinophils, neutrophils, macrophages, mast cells, monocytes, and platelets. Nedocromil sodium also inhibits neuronal pathways.[6,10]

Mediator release inhibitors are not effective in all patients; however, no factors have been identified to predict which patients are likely to respond. These agents are associated with mild adverse effects such as coughing or bad taste. Because of limited adverse effects, these drugs are considered suitable for long-term therapy early in the course of asthma. Clinical trials are ongoing to establish the role of nedocromil sodium in childhood asthma.[4,6]

2. Bronchodilator Drugs

Studies suggest that bronchodilators alone may not influence inflammation in the airway, may mask the underlying inflammation by briefly relieving the symptoms, and may allow greater exposure to allergens, irritants, and other environmental triggers.[4]

Beta-Adrenergic Agonists

Inhaled $beta_2$ adrenergic agonists are potent and effective bronchodilators. These drugs relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles. Most of these drugs have a rapid onset of action (within minutes) and are effective for 3 to 6 hours when the asthma is not severe. Despite controversy over their regular use in chronic asthma, they should be used as required for the relief of symptoms.

Although short acting inhaled $beta_2$-agonists are commonly prescribed on a regularly scheduled basis, the current recommendations stress their use only on an as needed basis. Because well-controlled asthma requires minimal use of short acting inhaled $beta_2$-agonists, increased use of these drugs indicates deteriorating control.[6] Moreover, recent information suggests that the combination of regular use of inhaled $beta_2$-agonist (albuterol) and allergen exposure may cause more airway inflammation than allergen exposure alone.[18]

Albuterol, bitolterol, pirbuterol, isoetharine, metaproterenol, and terbutaline are the short acting $beta_2$-agonists currently available. These agents are selective for the $beta_2$ adrenergic receptors in the lungs. Metaproterenol is less $beta_2$ adrenergic-specific than the other agents. Otherwise, little difference is noted among the group.[19] Nonselective beta-adrenergic agonists, such as isoproterenol, are associated with a high incidence of cardiovascular side effects and have no role in the treatment of asthma.

Short-acting oral beta-agonists are not indicated, with the exception of children unable to use the inhaled preparations.

The long acting inhaled $beta_2$-agonist, salmeterol, has recently been introduced. Salmeterol is not indicated for patients who can be managed with as needed inhalation of other beta-agonists. It is approved for use in patients with moderate or severe persistent asthma, and patients with nocturnal symptoms, in which scheduled $beta_2$-agonist therapy is required. **Salmeterol has a longer onset of action than other inhaled beta-agonists, and thus should not be used for management of an acute asthmatic attack.** Salmeterol is effective for the prevention of exercise-induced bronchospasm.[11]

In the patient who remains symptomatic despite therapy with inhaled steroids, the addition of salmeterol has been shown to be more effective in improving peak expiratory flow (PEF) than increasing the dose of inhaled steroid.[19,20] There is no evidence that salmeterol alone affects inflammation.[18]

Xanthine Derivatives

Although it is a less effective bronchodilator than the beta-adrenergic agonists, theophylline has often been the first-choice therapy for asthma in the United States. It can be administered orally or intravenously as aminophylline. Although the exact mode of action of theophylline is unclear, it directly relaxes the smooth muscle of the bronchi and pulmonary vessels, enhances diaphragmatic contractility, and stimulates central respiratory function. Clinical studies have shown that long-term treatment with theophylline can control asthma symptoms and improve lung function.[6] However, the narrow therapeutic index, the requirement for monitoring serum levels, and potential for significant adverse effects and drug interactions have led to reserving theophylline until other measures fail.[4,11,21]

A recent review[22] identified three indications for which theophylline provides a useful alternative to other therapies:

- Primary therapy for patients who cannot use an inhaled corticosteroid, such as young children.
- Primary therapy for patients who are more compliant with a regimen of oral medication than inhaled medication.
- Additive (Step 3) therapy for patients whose asthma is not adequately controlled with an inhaled corticosteroid.

The reader is referred to several articles[22-24] for a more

complete discussion of theophylline dosing and avoidance of adverse effects.

Anticholinergic Drugs

The use of anticholinergic agents in asthma dates back several centuries, but their side effects were unacceptable. The introduction of quaternary derivatives, such as ipratropium bromide, which are not absorbed into the circulation, has renewed interest in this group of drugs. These drugs block muscarinic receptors in airway smooth muscle, and thus inhibit vagal cholinergic tone, resulting in bronchodilation. They also block cholinergic reflex bronchoconstriction. Their onset of action is slower than that of beta-adrenergic agonists (peak effect in 1 hour), but their action is more prolonged, lasting up to 8 hours.[4]

Anticholinergic agents are less effective than beta-adrenergic agonists in the treatment of asthma, and are usually used in combination with other bronchodilators. Studies have shown additive effects when ipratropium is combined with nebulized beta-agonists in the emergency treatment of asthma.[4] The benefits of anticholinergic agents in the day to day management of asthma have not been established. Therefore, these agents are not included in this analysis.

Immunotherapy

Immunotherapy in the management of asthma is controversial.[25-28] The British Society for Allergy and Clinical Immunology has stated that immunotherapy is not recommended in asthma.[26] However, a recent meta-analysis of 20 randomized, placebo-controlled, double blind trials of allergen immunotherapy in asthma seem to support a role for it in selected patients.[25] Immunotherapy may be beneficial in patients with a documented allergy to house dust mites, pollen, animal dander, or mold. Importantly, the same study found systemic reactions occurred in a mean of 32% of all patients receiving active immunotherapy.

IV. Approach to Pharmacologic Therapy (Pediatric and Adult)

A step approach (Figure 1) delineates the manner in which the number of medications and the dosage of each medication are increased with increasing asthma severity. Progression to the next step is indicated when control cannot be achieved at the current step, despite assurance that the patient is using the medication correctly. The aim is to accomplish the goals of therapy with the least possible medication. Once control is sustained for several weeks or months, a reduction in therapy, a step down, should be considered to identify the minimum therapy required to maintain control.[6]

Seasonal Asthma

A patient has seasonal asthma when he or she has asthma symptoms due to seasonal exposure to an allergen. This may be intermittent in patients who are otherwise entirely asymptomatic between seasons, or it may occur as a seasonal worsening of persistent asthma. The severity varies from patient to patient and from season to season. Treatment will vary accordingly, but should follow the recommendations for the treatment of persistent asthma. The treatment should ideally start just before the expected season or upon the first symptoms and be stopped at the end of the season when symptoms or lung function abnormalities are no longer present.

Step 1: Intermittent Asthma

A patient has intermittent or mild asthma if he or she experiences episodes of cough, wheezing, or dyspnea less than once a week over a period of at least 3 months, and the exacerbations are brief, generally lasting only a few hours to a few days. Nocturnal asthma symptoms are infrequent and do not occur more than twice a month. Between exacerbations, the patient is asymptomatic and has normal lung function, i.e., a pretreatment baseline forced expiratory volume in one second (FEV_1) or PEF greater than 80% of predicted or personal best, and PEF variability of less than 20%.[6]

Intermittent asthma usually requires only a short-acting inhaled $beta_2$-agonist used as needed to relieve asthma symptoms. A short-acting inhaled $beta_2$-agonist, cromolyn sodium, or nedocromil may be used prophylactically prior to exercise. Cromolyn sodium or nedocromil may be used prophylactically before exposure to a known antigen (i.e., pet dander). Occasionally, more severe or prolonged exacerbations may require a short course of oral corticosteroids.

If medication is required more than once a week over a 3-month period, the patient should be moved to the next step of care, despite PEF measurements. Additionally, if the lung function between exacerbations becomes abnormal, the patient should be moved to the next step of care.[6]

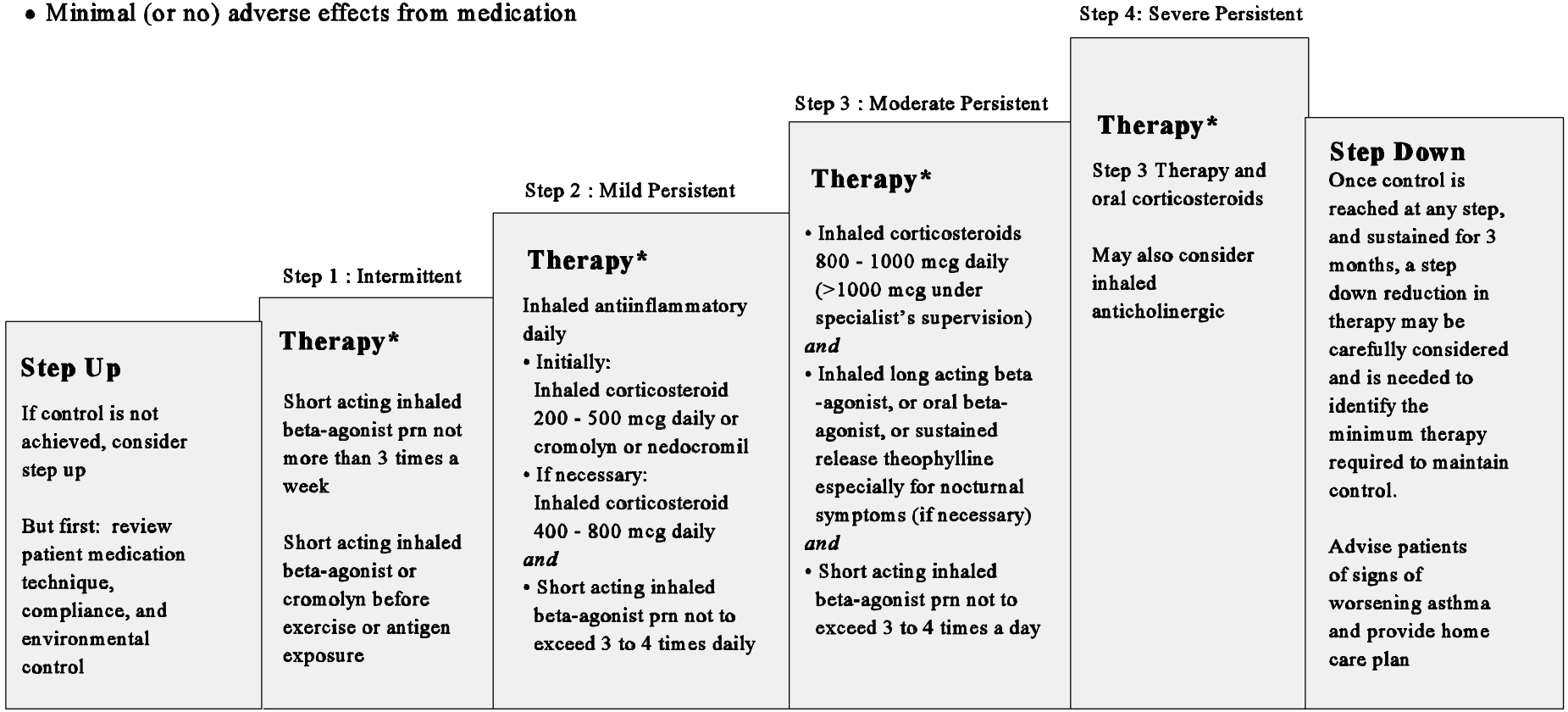
Figure 1: Chronic Asthma Management: A Stepwise Approach to Asthma Therapy

Outcome: Control of Asthma

- Minimal (ideally no) symptoms, including nocturnal symptoms
- Minimal (infrequent) episodes
- No emergency visits
- Minimal need for prn beta-agonist
- No limitations on activities, including exercise
  PEFR circadian variation < 20%
- (Near) normal PEFR
- Minimal (or no) adverse effects from medication

Outcome: Best Possible Results

- Least symptoms
- Least need for prn beta-agonist
- Least limitation of activity
- Least PEFR circadian variation
- Least adverse effects from medications



* ***All therapy must include patient information about prevention (including environmental control) as well as control of symptoms.***

Global initiative for asthma: global strategy for asthma management and prevention. National Institutes of Health, National Heart, Lung, and Blood Institute Publication 95-3659. Bethesda, MD. United States Department of Health and Human Services, 1995.

Step 2: Mild Persistent Asthma

Mild persistent asthma is present if the patient experiences symptoms at least once a week but less than once a day over the last 3 months and some exacerbations affect sleep and activity levels. Additionally, the patient may experience chronic symptoms that require symptomatic treatment almost daily and nocturnal asthma symptoms that occur more than twice a month. The patient with mild persistent asthma has a pretreatment baseline PEF of more than 80% of predicted or personal best and PEF variability of 20 to 30%. Cough variant asthma should be treated as mild persistent asthma.

Cromolyn sodium and nedocromil sodium are potential alternatives to inhaled steroids, but are generally recognized as less effective and significantly more costly than inhaled steroids. An initial dose of 200 to 500 mcg/day (88 to 176 mcg of fluticasone) is recommended for inhaled steroids. Use of a spacer device and mouth washing after inhalation is recommended when using inhaled corticosteroids to reduce oropharyngeal side effects. An inhaled short-acting beta$_2$-agonist should be available to take as needed to relieve symptoms, but should not be taken more than three to four times a day.

If symptoms persist, and the clinician is satisfied that the patient is using the inhaled medications correctly, the dose of inhaled corticosteroids should be increased up to 750 or 800 mcg/day. Alternatively, adding a long-acting bronchodilator to a dose of at least 500 mcg of inhaled corticosteroid may control nocturnal symptoms. The long-term efficacy of a combination of low-dose (< 500 mcg/day) inhaled corticosteroids and long-acting bronchodilators compared with higher doses of inhaled corticosteroids alone has not been adequately evaluated. However, adding inhaled salmeterol 50 mcg twice daily to inhaled beclomethasone dipropionate (BDP) 200 mcg twice daily was shown to be more effective than increasing the BDP dose to 500 mcg twice daily.[20]

If the patient's antiinflammatory therapy was initiated with cromolyn sodium or nedocromil sodium, and symptoms persist after 4 weeks of this initial treatment, then inhaled corticosteroids should be introduced. The inhaled corticosteroids may be initiated either instead of, or with the other medication to allow an overlap period.

Step 3: Moderate Persistent Asthma

Moderate persistent asthma is characterized by daily symptoms over a prolonged time or nocturnal asthma more than once a week. The patient with moderate persistent asthma has a pretreatment baseline PEF of more than 60% but less than 80% of predicted or personal best and PEF variability of 20 to 30%.

Inhaled corticosteroids are the drugs of choice and should be administered with a spacer device at a dose of 800 to 1,000 mcg/day (> 1000 mcg/day under specialist's supervision). Inhaled short-acting beta$_2$-agonists should be available to take as needed to relieve symptoms, but should not be used more than three to four times a day. Long-acting bronchodilators, in addition to the inhaled corticosteroids, may be considered, particularly to control nocturnal symptoms. The need for this additional intervention might better serve as indicator for referral to an asthma specialist. Therapeutic options for additional therapy include sustained-release theophylline, an oral slow-release beta$_2$-agonist, or a long-acting inhaled beta$_2$-agonist. Theophylline serum concentrations should be monitored, with a general therapeutic range of 5 to 15 mcg/mL.[6]

The role of anticholinergics (ipratropium bromide) in long-term therapy is not well established, but an anticholinergic may be considered as an alternative for patients who experience adverse effects, such as tachycardia or tremor, from inhaled beta$_2$-agonists.

Step 4: Severe Persistent Asthma

Severe persistent asthma is present if the patient experiences highly variable, continuous symptoms, and frequent nocturnal symptoms, has limited activities, and experiences severe exacerbations in spite of medication. The patient has a pretreatment baseline PEF of less than 60% of predicted or personal best and PEF variability greater than 30%. Complete control of asthma may not be possible. In severe persistent asthma, the goal of therapy becomes achieving the best possible results: the least symptoms, the least need for short-acting beta$_2$-agonist, the best PEF rates, the least circadian (night to day) variation, and the least side effects from medication. Therapy usually requires multiple daily controller medications. Primary therapy includes inhaled corticosteroids at high doses (more than 2,000 mcg/day) with a spacer.

A bronchodilator (i.e., sustained-release oral theophylline, an oral beta$_2$-agonist, a long-acting inhaled beta$_2$-agonist) is recommended with the inhaled corticosteroids. Regularly scheduled inhaled short-acting beta$_2$-agonists may be considered. A trial of inhaled anticholinergics may be considered, particularly for those patients who experience adverse effects from beta$_2$-agonists. Additionally, inhaled

short-acting beta$_2$-agonist should be available as needed up to three to four times a day to relieve symptoms.

Long-term oral corticosteroids should be used in the lowest possible dose (alternate or single daily doses after a 3- to 7-day burst). Persistent trials of high doses of inhaled corticosteroids administered with a spacer device should be attempted to reduce an oral corticosteroid dose. When patients are transferred from oral corticosteroids to high-dose inhaled corticosteroids, they should be monitored closely for evidence of adrenal insufficiency. The complexity of illness in patients with severe persistent asthma warrants referral to an asthma specialist.

Home management of exacerbations

Initiation of appropriate therapy at the earliest possible signs of deteriorating control of asthma is important in the successful management of asthma exacerbations. When patients are able to begin treatment at home, they not only avoid delays in treatment but also add to their sense of control over their asthma. The degree of care provided in the home depends on the health care professional's and patient's (or parents') experience and the availability of medications and emergency care. Ideally, all patients should have an action plan that outlines how and when to:

- Recognize signs of deterioration
- Start treatment
- Get medical care

Table 5 provides an important guide to correlation of signs and symptoms with asthma severity and PEF readings. Most asthma experts stress the importance of home PEF monitoring since both physicians and patients tend to underestimate the degree of airway obstruction in acute asthma.[28-32] However, one large study failed to show a reduction in morbidity with self monitoring of peak flow. The authors acknowledged that the most severe patients may have been excluded from the study and they are the most likely to have benefited from self monitoring.[32] Additionally, home PEF monitoring in children and adolescents should be interpreted cautiously because of the high probability of inaccuracy.[33] Figure 2 illustrates a recommended approach to home treatment.

Treatment with a short course of an oral steroid

At any step, "rescue" courses of oral steroids may be needed to control asthma exacerbations. Indications for an oral steroid may include the following[8]:

- Symptoms and PEF get progressively worse day by day
- PEF falls below 60% of the patient's best
- Nocturnal symptoms disturb sleep
- Morning symptoms persist until midday
- A diminishing response is noted with inhaled bronchodilator
- Emergency use of nebulized or injected bronchodilator is necessary

Adult patients should receive 30 to 60 mg daily (60 mg if currently taking oral or inhaled steroids) of a prednisone equivalent and continue for 2 days after full recovery, at which time the drug may be stopped or tapered. In children, a dose of 1 to 2 mg/kg should usually be used for 5 to 7 days; tapering of this dose is not needed in most situations.[8]

Stepdown: Reduction of maintenance therapy

Asthma is a variable disorder with spontaneous and therapy induced variations in severity. Antiinflammatory therapy has been shown to reduce asthma severity over the long term. Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be attempted to identify the minimum therapy required to maintain control. This tapering of therapy will help reduce the risk of side effects and enhance patient compliance with the treatment plan. The therapy reduction should be stepwise, following the reverse order of the previously described steps. Close monitoring of symptoms, clinical signs, and, as much as possible, lung function is necessary.[6,8]

Special Considerations for Children

Under diagnosis of asthma is a frequent problem, particularly in young children whose primary symptom is a cough. Additionally, some children may wheeze only when they have respiratory infections, and thus are often dismissed as having bronchitis or pneumonia although the signs and symptoms are more compatible with a diagnosis of asthma. For children less than 5 years of age, the PEF is either not attainable, or too dependent on fluctuating levels of attention and effort to be reliable. For these children, the history, with an assessment of the child's quality of life, and physical examination, are essential elements in decision-making. This information can be enhanced by symptom reports kept by the parent on a patient diary card.

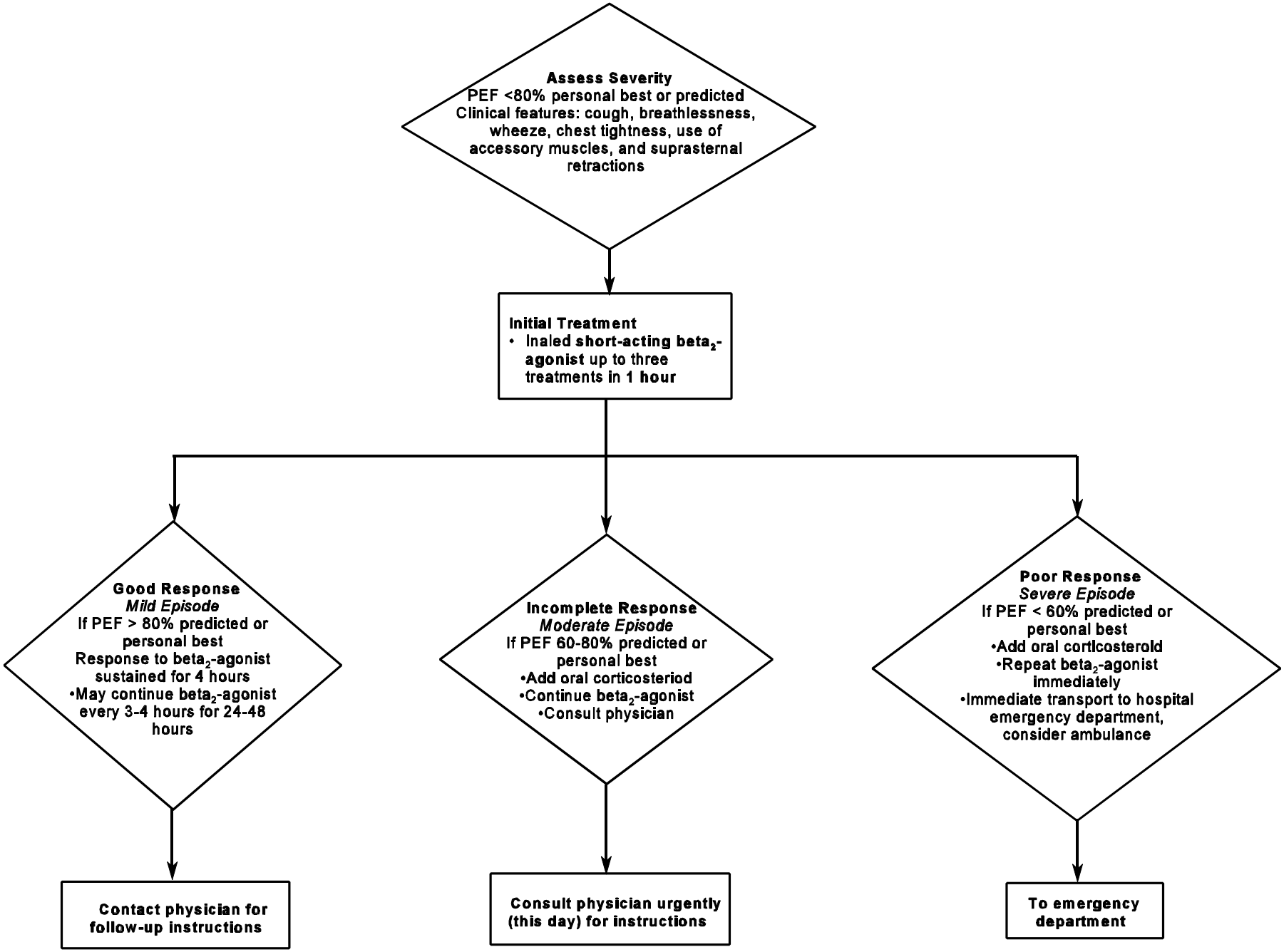
Viral upper respiratory tract infections are a common asthma trigger among children. Patients and parents need to be vigilant in adhering to the regular asthma medication treatment plans and be alert for early signs of exacerbation, so asthma medication may be started or increased

Table 5: Signs and Symptoms of Asthma Exacerbations*[,6]

	Mild	Moderate	Severe	Respiratory arrest imminent
Breathless	Walking Can lie down	Talking Infant-softer shorter cry; difficulty feeding Prefers sitting	At rest Infant-stops feeding Hunched forward	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Respiratory rate	Increased	Increased	Often > 30/min	
	Guide to rates of breathing associated with respiratory distress in awake children: *Age* — *Normal rate* < 2 months — < 60/min 2-12 months — < 50/min 1-5 years — < 40/min 6-8 years — < 30/min			
Accessory muscles and suprasternal retractions	Usually not	Usually	Usually	Paradoxical thoraco-abdominal movement
Wheeze	Moderate, often only end expiratory	Loud	Usually loud	Absence of wheeze
Pulse/min.	< 100	100-200	> 120	Bradycardia
	Guide to limits of normal pulse rate in children: Infants 2-12 months Normal rate < 160/min Preschool 1-2 years < 120/min School age 2-8 years < 110/min			
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10-25 mm Hg	Often present > 25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
PEF after initial bronchodilator % predicted or % personal best	Over 80%	Approx. 60-80%	< 60% predicted or personal best (< 100 L/min adults) or response lasts < 2 hrs	
PaO_2 (on air) and/or $PaCO_2$	Normal Test no usually necessary < 45 mm Hg	> 60 mm Hg < 45 mm Hg	< 60 mm Hg > 45 mm Hg: Possible respiratory failure (see text)	
SaO_2% (on air)	> 95%	91-95%	< 90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

*Note: The presence of several parameters, but not necessarily all, indicate the general classification of the exacerbation.

Figure 2: Management of Exacerbation of Asthma—Home Treatment[5]



immediately. For those individuals who deteriorate rapidly every time they have a viral respiratory infection, increasing the antiinflammatory treatment or to beginning a short course of oral corticosteroid therapy at the earliest sign of viral respiratory infection may be appropriate. The addition of antibiotics to treatment in the presence of viral upper respiratory infection does not have therapeutic benefit for asthma. However, antibiotics should be considered if signs of bacterial respiratory infection or sinusitis are present.[6]

Systemic absorption of low doses (less than 400 mcg/day in children) of inhaled corticosteroids with use of a large volume spacer does not affect linear growth.[34-38] A spacer must be used in all pediatric patients to minimize systemic absorption and oral candida infections. When inhaled corticosteroids are substituted for, or added to, treatment with cromolyn or nedocromil sodium to achieve control of asthma, an appropriate step down to consider is gradually reducing the inhaled corticosteroids and maintaining control with the cromolyn or nedocromil sodium. The inhaled corticosteroid may need to be restarted for seasonal asthma.

Currently, inhaled corticosteroids are the only controller medications that have been convincingly shown to be effective in children less than 3 years of age. Other medications have either not been studied thoroughly or produced uncertain results.[6] A therapeutic trial with alternative medications should be monitored very carefully, and the treatment should be stopped if a clear beneficial effect is not obvious. Theophylline may have increased risk of adverse side effects in infants with febrile illnesses because theophylline metabolism may be altered. Theophylline should only be considered if serum levels and potential drug interactions will be carefully monitored by the healthcare team. Individualized pharmacokinetic monitoring and counseling by a pharmacist may be useful in patients with fluctuating serum theophylline levels.

Spacers

Spacers are an important adjunct to aerosol delivery systems. These devices reduce the velocity and particle size of the aerosol thus minimizing oropharyngeal deposition. More medication penetrates deeper into the respiratory tract, minimizing drug side effects and maximizing overall drug activity. This is especially important for children and is recommended for adults. Use of a spacer greatly facilitates aerosol delivery for those patients who find it difficult to coordinate use of the metered dose inhaler with inhalation.

Important attributes of spacers include:

1. Delivery efficiency beyond oropharynx
2. Deposition in oropharynx
3. Closed system
4. Portability and convenience
5. Controlled inspiratory flow rate
6. Visual and tactile volume feedback
7. One-way valve
8. Compatibility with other systems
9. Usefulness with very young patients
10. Acquisition cost

Referral to an Asthma Specialist

Referral to a specialist should be considered for[8]:

(a) Patients in whom the diagnosis is in doubt.
(b) Patients with possible occupational asthma.
(c) Patients with asthma whose management is complex:
- those who have recently been discharged from the hospital.
- those with catastrophic suddenly severe (brittle) asthma.
- those with continuing symptoms despite high doses of inhaled steroids (800-1,200 mcg/day).
- those being considered for long term treatment with nebulized bronchodilators.
- pregnant women with worsening asthma.
- patients whose asthma is interfering with their lifestyle.

V. Education, Self Management, and Outreach

Studies have shown that asthmatics have major misconceptions about their disease and have misguided fears about inhaled steroids. It is common for patients to have significant concerns about side effects or even confusion with anabolic steroids. Many patients believe inhaled steroids should only be used occasionally to open airways, or will have the same side effects as anabolic steroids.

Patient education and patient-initiated action plans are important aspects of the treatment of asthma. Most published asthma management guidelines recommend that patients have a written action plan describing when and how to change medication during an exacerbation of asthma. The aim is to improve early detection and treatment of an exacerbation to reduce the risk of hospital admission and death that can occur when treatment is delayed. A recent study found that in patients with mild to moderately severe asthma, self management reduced incidents (days off work, unscheduled office visits, courses of oral steroids and antibiotics) and improved quality of life scores.[39]

Patient education involves a partnership between the patient and health care professionals that requires frequent revision and reinforcement. The aim is guided self-management: give patients the ability to control their own condition with guidance from the health care professionals.

Not all asthmatic DOD beneficiaries will have ready access to an asthma specialist. Facilities without asthma specialists on staff are strongly encouraged to develop case management programs in consultation with the appropriate specialty leaders. Examples of proactive, preventive case management programs recently started within DOD are presented in Appendix A.

VI. Analyses

This analysis addresses the therapeutic choices recommended at Steps 2 and 3 for both pediatric and adult patients. Step 4 therapy is not modeled as it is patient specific and requires referral to an asthma specialist. In addition, spacers were analyzed through attribute ranking by an expert panel.

Perspective

The models are developed from the perspective of the Department of Defense (DOD) as the payer of the healthcare benefits; therefore, lost productivity of non-active duty beneficiaries is excluded. Since the prevalence of asthma requiring Step 2 or 3 therapy in the active-duty population is assumed to be very low,[40] lost productivity for active duty members is excluded.

Assumptions:

- 1 year cost of treatment model.
- Head to head effectiveness studies of all the various types of controller medications are lacking; therefore, a common efficacy measure was selected from the available clinical trials for both Step 2 and 3 therapies. The efficacy measure selected for Step 2 therapy is the percent of symptom-free days; for Step 3, the measure is lack of nocturnal awakenings. The question of what is the best measure of efficacy of asthma therapy is yet to be defined.[41,42]
- All inhaled corticosteroids are assumed to be equipotent on a microgram basis, with the exception of fluticasone, which is twice as potent as the other inhaled corticosteroids.[3,12,13]
- Using percent symptom-free days reported in clinical trial data as the outcome measure, no dose-response effect was seen with the inhaled corticosteroids. The response to the medications more closely resembled a threshold effect: at any dose, the medication either worked or did not work. This effect also was seen with cromolyn and nedocromil. For this reason, the inhaled corticosteroids, cromolyn, and nedocromil were given the same efficacy.
- The corticosteroid inhaler is used with a spacer. If the spacer is not part of the inhaler unit, the cost of one spacer per year is included.
- Adverse effects of cromolyn sodium and nedocromil are mild and do not incur a treatment cost to the DOD. Use of cromolyn capsules includes the cost of a Spinhaler unit; use of cromolyn nebulizer solution includes the cost of a home nebulizer.
- The only adverse effect of inhaled corticosteroids that incurs a treatment cost to the DOD is oral candida infection. The cost of treating an oral candida infection is the same for all the steroids, differing only in the probability of occurrence. Oral candida infections with the use of inhaled corticosteroids depend on several factors: the patient's compliance with using a large volume spacer, rinsing the oral cavity with water after using the inhaler, the patient's immune status, and perhaps, the dose of steroid.
- Adverse effects of both oral and inhaled beta-agonists are minor and do not incur a treatment cost to the DOD.
- Patients receiving theophylline are assumed to be titrated to a dose that would result in a serum therapeutic level in the range of 10 to 20 mcg/mL. Currently, a lower range (5 to 15 mcg/mL) is recommended; the available studies used the higher range of serum levels.
- In the military health care system, acute adverse effects of theophylline will be treated in the emergency department, resulting in either discharge to outpatient follow-up or hospitalization. Hospitalization cost is based on diagnosis-related group (DRG) rate for the central Texas area. This rate was varied by 5% to reflect the differential rates throughout the country. Emergency department treatment includes a serum theophylline level and a chemistry panel. The probability that a patient experiencing adverse effects from theophylline will seek treatment for those effects is unknown, and depends on the type and severity of the effects. A range of 20% to 80% was used in the model based on expert opinion.
- Treatment failure costs used in the analysis of Step 2 therapy are the same for all drug regimens, differing only in the probability of occurrence (1- effectiveness).

These costs include an emergency department visit, resulting in either outpatient follow-up or hospitalization, then outpatient follow-up. The probability that a patient who experiences treatment failure on Step 2 therapy (symptomatic days) will seek treatment is not known; a range of 20% to 80% was used in the model based on expert opinion. The diagnosis related group (DRG) for uncomplicated asthma, DRG 096, was used for the cost of hospitalization. This rate was varied by 5% to reflect the difference in rates across the country.

- All inhaled steroids are given on a twice daily dosing schedule.[15-17,43]
- The frequency of the dosing regimen (i.e., QD, BID, TID, QID) was used as the compliance measure, not the number of puffs per dose. Compliance with a regimen requiring multiple administrations from the inhaler at one time is unknown. Mann et al[11] studied a small group of patients who were prescribed 4 puffs of an inhaled corticosteroid twice daily. Study results showed that patients received an average of 6.8 puffs per day versus the prescribed dose of 8 puffs per day. The precise clinical relevance of this modest difference is unknown.
- The precise dropout rate for patients using theophylline is unknown. Many clinical trials exclude from analysis those patients who could not tolerate the drug during the titration phase of the study; therefore, the reported dropout rates from these trials underestimate the true dropout rate.
- The probability of patients experiencing adverse effects from theophylline that require treatment was taken from clinical trial data. The probability seen in practice depends on several factors, including the patient's compliance with the dosing regimen, drug-drug interactions, the patient's perception of the seriousness of the adverse effects, and the patient's individual pharmacokinetic profile, and may differ from that reported in clinical trials.
- Pediatric dosing regimens were stratified into 2 age groups: children $\leq$ 5 years of age and children > 5 years of age. This stratification was done to reflect the dose and dosage form used by the different age groups (i.e., theophylline liquid vs theophylline sustained release tablets or capsules) and the size of the child. For children $\leq$ 5 years, a 14 kg child was used as the representative size; a 25 kg child was used for the older age group.
- Acquisition cost of the drugs used in the analysis reflects the best price available to the DOD on June 20, 1996.
- Since the marginal cost of physician visits, laboratory tests, radiological studies, and emergency room visits are unknown for the DOD, the CHAMPUS maximum allowable charge (CMAC) was used as a proxy. These values were varied by 5% to reflect the difference in rates across the country.

Table 6: Variable List

Variable	Point estimate	Range	Reference
Initial visit (IV)	$104.00	± 5 %	CMAC*
Phone follow-up (PFU)	$12.50	± 5 %	CMAC*
Short follow-up visit (SFU)	$31.25	± 5 %	CMAC*
Long follow-up visit (LFU)	$50.00	± 5 %	CMAC*
Office spirometry (Sp)	$28.44	± 5 %	CMAC*
Serum theophylline level (TL)	$37.50	± 5 %	CMAC*
Home nebulizer	$173.24	± 5 %	CMAC*
Spinhaler	$8.12		Federal Supply Schedule
Spacer	$7.00		Federal Supply Schedule
Nystatin liquid 60 mL	$0.59		Federal Supply Schedule
Cost of ED visit for theophylline adverse effects (cEDT)	$283.00	± 5 %	44

Variable	Point estimate	Range	Reference
Probability of theophylline adverse effects (pEDT)	0.12	0.036 - 0.21	45-53
Probability of seeking treatment for theophylline side effects (pSTT)	0.4	0.2 - 0.8	Expert opinion
Cost of hospitalization for theophylline adverse effects (cHT)	$2631	± 5 %	DRG 450
Probability of hospitalization for theophylline adverse effects (pHT)	0.00078	± 5 %	22, 49, 51, 52
Probability of ICU admission for theophylline adverse events	0.08 × pHT	0.05 - 0.26	22, 49, 51, 52
Cost of ICU admission for theophylline adverse events (in addition to hospitalization costs)	$2000	$1500 - $2500	Estimate
Cost of ED visit for treatment failure (cEDF)	$236.00	± 5 %	54, 55
Probability of seeking treatment for treatment failure (pSTF)	0.4	0.2 - 0.8	Expert opinion, 56-60
Cost of hospitalization for treatment failure (cHF)	$3951	± 5 %	DRG 096
Probability of hospitalization for treatment failure (pHF)	0.082 × (1-effectiveness)	± 5 %	61
Compliance with dosing regimen (C)			62, 63
QD	0.87	0.76 - 0.98	
BID	0.81	0.64 - 0.98	
TID	0.77	0.52 - 0.9	
QID	0.39	0.15 - 0.63	
Probability of oral candida infection (pCND)			64-74
Beclomethasone	0.049	0.0076 - 0.09	
Budesonide	0.049	0.0076 - 0.09	
Flunisolide	0.049	0.0076 - 0.09	
Fluticasone	0.04	0.01 - 0.07	
Triamcinolone	0.049	0.0076 - 0.09	
Efficacy (% symptom-free days) (ES)			64-92
Beclomethasone	54.5%	26 - 83%	
Budesonide	54.5%	26 - 83%	
Flunisolide	54.5%	26 - 83%	
Fluticasone	54.5%	26 - 83%	
Triamcinolone	54.5%	26 - 83%	
Cromolyn	54.5%	26 - 83%	
Nedocromil	54.5%	26 - 83%	
Theophylline	61.5%	40 - 83%	

Variable	Point estimate	Range	Reference
Drop-out rate (pDr)			20, 64-92
Beclomethasone	0.048	0.015 - 0.082	
Budesonide	0.048	0.015 - 0.082	
Flunisolide	0.048	0.015 - 0.082	
Fluticasone	0.05	0.015 - 0.06	
Triamcinolone	0.048	0.015 - 0.082	
Cromolyn	0.01	0 - 0.02	
Nedocromil	0.01	0 - 0.02	
Theophylline	0.106	0.04 - 0.18	
Salmeterol	0.024	0.012 - 0.036	
Albuterol LA	0.04	0.03 - 0.05	
Efficacy (Probability of no nocturnal awakenings) (EN)			81-83, 85, 86, 91-92
Albuterol LA tablets	0.785	0.71 - 0.86	
Salmeterol inhaler	0.925	0.85 - 1	
Theophylline	0.785	0.71 - 0.86	

* CMAC = CHAMPUS maximum allowable charge

Step 2 Therapy

Cost Effectiveness of Drug A = C/E_A

$$C/E_A = \frac{\Sigma \text{Cost of Treatment}_A + \Sigma \text{ Cost of Side Effects}_A + \Sigma \text{ Cost of Treatment Failure}_A + \Sigma \text{ Opportunity Cost}_A}{\text{Effectiveness}_A}$$

$IV + PFU + (3 \times SFU) + (4 \times Sp) + (2 \times TL) + DC_A +$	(Cost of treatment) +
$pCND_A\ [(2 \times SFU) + NY] +$	(Cost of candida infection) +
$pSTT[pEDT \times [cEDT + (2 \times TL) + (pHT \times cHT) + (pICU \times cICU) + LFU]] +$	(Cost of theophylline adverse effects) +
$pSTF[(1 - Eff_A) \times (cEDF + (pHF \times cHF) + LFU + Sp)$	(Cost of treatment failure)
$[ES_A \times C \times (1 - pDR_A)]$	(Effectiveness)

Key to Abbreviations:

IV = Initial visit cost
PFU = Phone follow-up visit cost
SFU = Short follow-up visit cost
Sp = Cost of office spirometry
TL = Serum theophylline level cost
DC_A = Drug acquisition cost (includes cost of spacer, or nebulizer, or spinhaler, if needed)
$pCND_A$ = Probability of oral candida infection for drug A
NY = Cost of 60 mL of nystatin liquid
pSTT = Probability of seeking treatment for theophylline side effects
pEDT = Probability of experiencing theophylline side effects
cEDT = Cost of treating theophylline side effects in the emergency department
pHT = Probability of hospitalization for theophylline adverse effects
cHT = Cost of hospitalization for theophylline adverse effects (non-intensive care)
pICU = Probability of ICU admission for theophylline adverse effects
cICU = Cost of ICU admission for theophylline adverse effects (additional cost)
LFU = Long follow-up visit cost

pSTF = Probability of seeking treatment for treatment failure
Eff_A = Effectiveness of drug A (i.e., the denominator of the equation)
cEDF = Cost of emergency department visit for treatment failure
pHF = Probability of hospitalization for treatment failure
ES_A = Efficacy of drug A (% symptom-free days)
C = Compliance with dosing regimen
pDr_A = Dropout rate for drug A

Equation Components:

Cost of $Treatment_A$ = Cost of physician visits + Cost of office spirometry + Cost of labs + Drug cost

Cost of physician visits (cPV) = Initial visit + Phone call @ 2 weeks post initial visit + short office visits @ 6 weeks, 6 months, and 1 year post initial visit (note - theophylline model includes an additional short office visit for titration purposes in place of the phone call at 2 weeks post initial visit)

$$cPV = IV + PFU + (3 \times SFU)$$

Cost of office spirometry = initial visit, 6 weeks, months, and 1 year post initial visit = $4 \times Sp$

Cost of labs = 2 serum theophylline levels per year (if applicable) = $2 \times TL$

Drug cost (DC_A) = Drug acquisition cost + Spacer* + Nebulizer* + Spinhaler* (* If applicable)

Cost of Side Effects (SE_A)
Corticosteroids
SE_A = Probability of oral $candidiasis_A \times$ Cost of candidiasis treatment

$SE_A = pCND_A \times$ (Cost of 2 additional short office visits + Cost of 60 mL of nystatin liquid)

$SE_A = pCND_A \times [(2 \times SFU) + NY)]$

Theophylline
SE_A = Probability of seeking treatment for theophylline side effects × Probability of experiencing theophylline side effects × (Cost of emergency department visit + cost of hospitalization + cost of clinic follow-up)

$SE_A = pSTT \times \{pEDT \times [cEDT + (2 \times TL) + (pHT \times cHT) + (pICU \times cICU) + LFU]\}$

Cost of $Treatment\ Failure_A$ (cTF_A) = (Probability of treatment failure × Cost of treatment failure) × Probability of seeking treatment for treatment failure

cTF_A = Probability of seeking treatment for failure × {(1 - $Effectiveness_A$) × [Cost of emergency department visit for treatment failure + (Probability of hospitalization × Cost of hospitalization) + Cost of long office visit + Office spirometry cost]}

$cTF_A = pSTF \times \{(1\text{-}Eff_A) \times [cEDF + (pHF \times cHF) + LFU + Sp]\}$

$Effectiveness_A$ (Eff_A) = $Efficacy_A \times$ Compliance with dose regimen × (1 - $Drop\ out\ rate_A$)

Efficacy measure for Step 2 therapy is the percent of symptom-free days.[41]

$$Eff_A = ES_A \times C \times (1 - pDr_A)$$

Table 7: ***Pediatric Step 2 Therapy Results (≤ 5 years of age) and Preferred Drug List***

Drug Regimen	Average C/E*	95% Confidence Interval*
Triamcinolone Inhaler @ 200 mcg/day	$617.19	$603.19-631.19
Beclomethasone Inhaler @ 168 mcg/day	$650.33	$636.33-664.33
Triamcinolone Inhaler @ 400 mcg/day	$662.44	$648.44-676.44
Theophylline Liquid† 14 kg child @ 80 mg QID	$676.58	$665.58-687.58
Beclomethasone Inhaler @ 336 mcg/day	$711.47	$696.47-726.47
Fluticasone Inhaler @ 88 mcg/day	$986.88	$967.88-1005.88
Fluticasone Inhaler @ 176 mcg/day	$1,393.06	$1367.06-1419.06
Cromolyn Caps @ 20 mg TID	$1,688.19	$1656.19-1720.19
Cromolyn Nebs @ 20 mg TID	$2,359.45	$2316.45-2402.45
Cromolyn Caps @ 20 mg QID	$5,166.19	$5041.19-5291.19
Cromolyn Nebs @ 20 mg QID	$5,765.85	$5626.85-5904.85
Remain on Step 1 Therapy	$5,832.49	$5718.49-5946.49

* Derived from 1000 trials of Monte Carlo analysis.
† Based on international guidelines, theophylline is third-line therapy for step 2 treatment.

Table 8: ***Pediatric Step 2 Therapy Results (> 5 years of age) and Preferred Drug List***

Drug Regimen	Average C/E*	95% Confidence Interval*
Theophylline SR 300 mg BID†	$335.46	$333.46-337.46
Flunisolide @ 500 mcg/day	$622.14	$608.14-636.14
Triamcinolone @ 400 mcg/day	$662.44	$648.44-676.44
Beclomethasone @ 336 mcg/day	$711.47	$696.47-726.47
Fluticasone @ 88 mcg/day	$986.88	$967.88-1005.88
Fluticasone @ 176 mcg/day	$1,393.06	$1367.06-1419.06
Nedocromil @ 3.75 mg TID	$1,440.68	$1412.68-1468.68
Cromolyn Caps @ 20 mg TID	$1,688.19	$1656.19-1720.19
Cromolyn Inhaler @ 3.2 mg TID	$1,693.23	$1674.23-1712.23
Nedocromil @ 3.75 mg QID	$3,654.95	$3558.95-3750.95
Cromolyn Inhaler @ 3.2 mg QID	$4,330.60	$4,216.60-4444.60
Cromolyn Caps @ 20 mg QID	$5,166.19	$5041.19-5291.19
Step 1 therapy only	$5,832.49	$5718.49-5946.49

* Derived from 1000 trials of Monte Carlo analysis.
† Based on international guidelines, theophylline is third-line therapy for step 2 treatment.

Table 9: ***Adult Step 2 Therapy Results and Preferred Drug List***

Drug Therapy	Average C/E*	95% Confidence Interval*
Theophylline SR 300 mg BID†	$335.46	$333.46-337.46
Theophylline SR 400 mg BID†	$391.41	$388.41-394.41
Flunisolide @ 1000 mcg/day	$672.32	$657.32-687.32
Triamcinolone @ 800 mcg/day	$752.92	$736.92-768.92
Beclomethasone @ 672 mcg/day	$833.74	$816.74-850.74
Fluticasone @ 220 mcg/day	$1,062.41	$1041.41-1083.41
Nedocromil @ 3.75 mg TID	$1,440.68	$1412.68-1468.68
Cromolyn Inhaler @ 3.2 mg TID	$1,693.23	$1674.23-1712.23
Fluticasone @ 440 mcg/day	$1,937.66	$1,903.66-1971.66
Nedocromil @ 3.75 mg QID	$3,654.95	$3558.95-3750.95
Cromolyn Inhaler @ 3.2 mg QID	$4,330.60	$4216.60-4444.60
Step 1 therapy only	$5,832.49	$5718.49-5946.49

* Derived from 1000 trials of Monte Carlo analysis.
† Based on international guidelines, theophylline is third-line therapy for step 2 treatment.

Step 3 Adjunctive Therapy (Pediatric and Adult)

Assumptions:

- Step 3 adjunctive therapy is independent of Step 2 therapy and patients are receiving adequate Step 2 therapy.
- Patients with treatment failure on Step 3 therapy (nocturnal awakenings) do not seek additional treatment either through the emergency department or the clinic.

$$C/E_A = \frac{DC_A + (2 \times TL) + SFU + pSTT\,[pEDT \times [cEDT + (2 \times TL) + (pHT \times cHT) + (pICU \times cICU) + LFU]]}{EN_A \times C \times (1 - pDR_A)}$$

Key to Abbreviations:
DC_A = Drug acquisition cost
TL = Serum theophylline level cost
SFU = Short follow-up visit cost
pSTT = Probability of seeking treatment for theophylline side effects
pEDT = Probability of experiencing theophylline side effects
cEDT = Cost of treating theophylline side effects in the emergency department
pHT = Probability of hospitalization for theophylline adverse effects
cHT = Cost of hospitalization for theophylline side effects (non-intensive care)
pICU = Probability of ICU admission for theophylline side effects
cICU = Cost of ICU admission for theophylline side effects
LFU = Long follow-up visit cost
EN_A = Efficacy of drug A (lack of nocturnal awakenings)
C = Compliance with dosing regimen
pDR_A = Dropout rate for drug A

Table 10: ***Step 3 Adjunctive Therapy Results and Preferred Drug List***

Drug Regimen	Average C/E*	95% Confidence Interval*
Theophylline 300 mg BID	$256.68	$255.68-257.58
Theophylline 400 mg BID	$302.10	$300.10-304.10
Albuterol LA 4 mg BID	$342.35	$340.35-344.35
Salmeterol @ 50 mcg BID	$485.03	$482.03-488.03
Theophylline Liquid @ 14 kg child @ 80 mg QID	$663.44	$651.44-675.44
Albuterol LA 8 mg BID	$684.69	$680.69-688.69

* Derived from 1000 trials in Monte Carlo analysis.

Spacers

Spacers were evaluated on the basis of the following attributes by an expert panel of physicians using a Likert scale of 1-10 representing most important to least important. Panel members represented Army, Navy, and Air Force and included a family practice physician, allergist, and pediatric pulmonologist.

1. Delivery efficiency beyond oropharynx
2. Deposition in oropharynx
3. Closed system
4. Portability and convenience
5. Controlled inspiratory flow rate
6. Visual and tactile volume feedback
7. One-way valve
8. Compatibility with other systems
9. Usefulness with very young patients
10. Acquisition cost

The spacer receiving the best overall score was InspirEase®.

VII. Results

Step 2 Therapy:

Sensitivity Analysis

Monte Carlo analysis of the variables listed in Table 6 produced slight changes in the absolute value of the average cost-effectiveness ratio, but no changes in the relative ranking of the therapies. The Monte Carlo analysis was run over 1000 trials, with the point estimates varied randomly within the ranges listed in Table 5.

Compliance with the dosing regimen was the driving force of the model. As the compliance improved, the average cost-effectiveness improved. This is clearly demonstrated with the results for cromolyn and nedocromil by comparing the cost-effectiveness ratio for three times a day dosing to four times a day dosing.

Univariate analysis of the individual variables produced the same effect as the Monte Carlo analysis.

Discussion

The major limitation of this model, and any other model of asthma treatment, is attempting to model the clinical uncertainties of the disease. A "gold standard" for measuring both efficacy and effectiveness of asthma drug treatment has not been identified and evaluated with the available therapies. This model used symptom-free days as the clinical outcome measure for Step 2 therapy, and no difference was found in the study results to differentiate the various inhaled corticosteroids. Morning percent predicted peak flow was considered for the outcome measure, but was not included in enough studies to make the data relevant.

Patient compliance with a drug regimen that involves multiple inhalations per dose is unknown, and was not included in this model. If compliance with multiple inhalation dose regimens was known, it could change the results of the model, as compliance with the dosing regimen was the major factor driving the model.

The option to do nothing (i.e., remain on Step 1 therapy when Step 2 therapy is indicated) is included for comparison purposes. This option is significantly less cost-effective than any of the available controller therapies.

Mediator-release inhibitors are the least cost-effective choices for Step 2 therapy.

Step 3 Therapy

Sensitivity Analysis
Monte Carlo analysis of this model over 1000 trials did not produce any changes in the relative ranking of the therapies, only in the absolute value of the average cost-effectiveness. This model was sensitive to drug acquisition cost due to the large difference in cost per dose between theophylline and the newer agents.

Discussion
Successful adjunctive therapy resulting in control or lessening of nocturnal symptoms is dependent on patient compliance with the treatment regimen. If the patient can tolerate theophylline, it is the most cost-effective regimen; otherwise, a long-acting beta-agonist should be employed.

VIII. Tri-Service Formulary (TSF) Selections

While this document addresses the management of all severities of asthma, TSF selections address only primary care requirements. It is assumed that most patients with asthma beyond Step 3 (moderate persistent) in severity will require consultation by an asthma specialist. Formulary selections in this category may be institution specific and are therefore left to the local Pharmacy & Therapeutics Committee.

A. Antiinflammatory Drugs

Corticosteroids

Oral prednisone (5 and 20 mg tablets) will remain on the TSF. Prednisone oral solution 5 mg per 5 mL and prednisolone oral solution 15 mg per 5 mL are added to the TSF for pediatric dosing when oral steroids are needed. Prednisone and prednisolone are equipotent (the same dose is used with either drug) and therapeutically equivalent. The two strengths are included on the TSF for dosing convenience. Prednisone 5 mg per 5 mL was selected over prednisolone 5 mg per 5 mL because it is less expensive.

Selection of an inhaled oral corticosteroid is based on the results of the cost-effectiveness analysis of Step 2 therapies (Tables 7-9). For higher daily doses, flunisolide is the most cost-effective agent and is added to the TSF. For the lowest daily dose analyzed, triamcinolone is the most cost-effective agent and is added to the TSF. Beclomethasone oral inhaler is deleted from the TSF.

Mediator Release Inhibitors

The mediator release inhibitor agents (cromolyn and nedocromil) are much less cost-effective antiinflammatory agents than the inhaled corticosteroids. While these agents may be useful in patients who cannot or will not use inhaled corticosteroids, they are not included on the TSF.

B. Bronchodilator Drugs

Short-acting inhaled beta-adrenergic agonists

Because the use of a short-acting inhaled beta-agonist is limited to use as needed, the selection is based on acquisition cost[19]; the TSF selection is albuterol oral inhaler. Short-acting oral beta-agonists are rarely used in asthma, therefore, oral terbutaline tablets 5 mg are deleted from the TSF.

Xanthine derivatives

Xanthine derivatives are effective second or third line agents when appropriately used and monitored, especially in patients who have difficulty in using a metered dose inhaler or prefer to use an oral medication. Theophylline liquid (80 mg per 15 mL), theophylline sustained release 50, 200, and 300 mg as SloBid™ Gyrocaps are added to the TSF. Most military treatment facilities use Theodur® or SloBid™ for their sustained release theophylline; SloBid's acquisition cost is less than Theodur's cost.

Anticholinergic drugs

Due to the lack of efficacy data regarding the use of anticholinergic drugs in treating asthma at Steps 1-3, these agents cannot be recommended for addition to the TSF. Anticholinergic drugs may be useful in Step 4 therapy, and may be considered for local formulary addition.

Long-acting beta adrenergic agonists:

Oral

While these agents are competitive in terms of cost-effectiveness at a low dose (Table 10), most patients require a higher dose to relieve their symptoms. At higher doses, they become the least cost-effective alternative for Step 3 therapy. Therefore, these agents are not included on the TSF.

Inhaled

Salmeterol currently is the only agent in this category. It is less cost-effective than theophylline sustained

release given once or twice daily and is not included on the TSF.

C. Spacers

Based on the results from the expert panel, InspirEase® received the best score from all panelists and is selected for the TSF.

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APPENDIX A: DOD Asthma Case Management Programs

I. National Naval Medical Center (NNMC)

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A study was undertaken in the National Capitol Region in 1993 to assess the impact of an integrated asthma program based on currently recognized best practice guidelines. NNMC served as the intervention hospital and four other military hospitals in the region served as controls. Measurable improvements in outcome were demonstrated in a short period of time. Implementation involved three major initiatives:

1. Educational Program

A broad education program designed to familiarize all pediatric care providers was started. The curriculum incorporated the four major components of NHLBI guidelines: pharmacologic management, objective measures of lung function, environmental control, and patient education. Emphasis was placed on minimizing or eliminating flares by appropriate patient education, long term management, and follow up. The management of acute flares was de-emphasized. Specific teaching aids included pocket-sized cards outlining the treatment of acute asthma in the clinic or emergency department (ED) and a wall card outlining the approach to chronic management. These tools were intended to promote retention of the core material. Correct metered dose inhaler technique and the use of age-appropriate spacer devices were stressed repeatedly at morning conferences, nursing inservices, and medical student teaching conferences.

2. Outpatient Management

A specific clinic was established in order to provide evaluation and continuing follow-up of children with asthma. Providers in the Pediatric Acute Care Clinic and the Emergency Department were encouraged to refer patients to this clinic if they presented with an acute flare and had no identified primary care provider. Self referral was also possible.

During the initial visit an assessment of the patient's current functional status was made, lung function data was collected, and educational deficits were addressed. Educational efforts were directed at self management. Metered dose inhaler technique was reviewed and the patient and parent were given specific written instructions which covered maintenance therapy as well as therapy for flares. Phone contact was encouraged and phone numbers were included in the handout. These same resources were made immediately available to physicians working in the Pediatric Acute Care Clinic by physically locating them in the center of that clinic. The nursing staff was familiarized with the overall importance of treating asthma as a chronic disease, the specifics of good inhaler technique, and specific information on how to assist parents in obtaining a nebulizer on an expedited basis from local vendors, if needed.

3. Inpatient Management

The provision of self management education after a detailed assessment of the patient and families current self management skills, and identifying a mechanism for long term follow-up also included patients admitted to the inpatient service. Patients remained on the general pediatric service. At discharge patients were offered the opportunity to be followed in a resident's continuity clinic or referred back to their previous continuity provider.

II. Keesler Air Force Base

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Subsequent to the publication of the DOD quality management review of pediatric asthma in May 1995 the 81st Medical Group at Keesler Air Force Base developed a model disease management initiative known as **AIR Keesler** (Asthma Is Reversible).

An interdisciplinary working group was formed in August 1995 focusing on three areas: staff education, patient

education, and care coordination/research services. Implementation began in January 1996.

Staff Education

1. The Care Coordinator attended the Asthma Patient Education Program at National Jewish Medical Center, a leading authority in the treatment of respiratory illness.

2. The Internal Medicine, Primary Care, ED, Pediatric, and other provider staff at Keesler Medical Center were trained on the National Heart, Lung, and Blood Institute guidelines for asthma through multiple educational forums. Keesler Medical Center conducted a Continuing Education Program on asthma. Attendees included nurses, technicians, respiratory therapists, and pharmacy personnel.

Patient Education

1. The children most severely affected by asthma were identified by history and chart reviews for symptoms, inpatient admissions/intubations, and ER presentations, and were selected for care coordination.

2. Subsequent to the completion of the training program at National Jewish Medical Center, **AIR Keesler's** Care Coordinator provided extensive one-on-one education for families of these children. Families were provided information on managing the care of their child during acute episodes and adjusting their lifestyle to support a child with a chronic illness.

3. The Asthma Working Group developed a four-class dual group patient education series providing information to children and their parents. The interdisciplinary faculty utilizes a variety of teaching activities from lectures and hands-on demonstration of equipment to puppet shows and the "Bronchie the Bronchiasaurus" Supernintendo game that teaches asthma self management skills. Advertisements for these classes were mailed to the target population and formal classes began in January 1996.

Care Coordination/Research Tools and Methodology

1. Standard disease codes were used to identify children admitted to the medical center with asthma. A computer program was developed to search the electronic ED log for patients whose primary complaint was "asthma, wheezing, or reactive airway." The Care Coordinator is notified daily of all asthma related ED presentations, clinic visits, and admissions.

2. A standardized documentation form was implemented in late February 1996 to provide a uniform approach to asthma management and to document all aspects of clinical care recommended by national guidelines. This form was used to conduct a retrospective review of medical records providing data to evaluate changes in practice patterns and compare clinical/cost outcomes. A database is in the final phase of development for compiling data collected with these forms.

3. Allergen skin testing of asthmatic children was emphasized as a priority. Knowing which substances trigger an asthmatic attack provides options to prevent exposure or minimize their effect.

4. Nebulizers were directly issued to patients with moderate/severe asthma. A contract was established with the manufacturer reducing the amount paid from $173.24/unit (CHAMPUS allowable) to $72.35/unit (a 58% cost saving). Providing the nebulizer enabled patients to be treated at home when symptoms first appeared rather than waiting until they become severe enough to require hospitalization. The costs of preventive care avoided the higher cost of a hospital stay.

5. A pager system is under development to facilitate contact between the target population of moderate/severe asthmatics and an AIR Keesler contact point (the care coordinator during normal duty hours/pediatric resident after hours).

a. An emergency care plan (ECP) format is being developed that can be individualized for each patient. The ECP instructs the family to page AIR Keesler if the treatments recommended do not improve the peak flows or symptoms.

b. The AIR Keesler contact point, after reviewing the clinical history, will adjust treatment and expedite follow-up through the ED or Pediatric Clinic as appropriate. They will also make a medical record entry to document care provided.

c. Coordination of the ECP and beeper systems is in progress. The 81st Communications Squadron can help monitor the pager system's use and reliability by providing listings of the phone numbers and time/date when the designated pager has been activated.

6. Multiple research protocols were developed to evaluate the clinical impact and cost effectiveness of **AIR Keesler**. Outcome measures include quality of life metrics, in-home measurement of lung function, use of peakflow meters, and medication compliance metrics based on refill patterns and frequency.

APPENDIX B

DRUG USAGE EVALUATION MONITORING FORM

DISEASE STATE _____ DRUG _____

SURVEY PERIOD: FROM: _____ TO: _____

COLLECTED BY: _____ DATE OF COLLECTION: _____

ATTENDING PHYSICIAN _____ SERVICE _____

PATIENT NAME _____ SSN _____ AGE _____

SEX _____ WEIGHT _____ ALLERGIES _____

ELEMENT	STD*	MET STD	COMMENT
1. All patients with more than mild, intermittent asthma are maintained on an antiinflammatory medication (preferably an inhaled corticosteroid).	100%	Y/N	Medical record reflects adverse events reported through MTF ADR reporting system.
2. All patients receive both oral and written instructions for using their medications and can demonstrate the appropriate use of their medications.	100%	Y/N	
3. All patients have a written home management plan for exacerbations that includes self-monitoring.	100%	Y/N	

* Standard to be adjusted by medical treatment facility Pharmacy &Therapeutics Committee.

Tri-Service Formulary Quick Reference Guide

Antimicrobials / Antifungals
*amoxicillin oral suspension and caps
*Bactrim™/Septra® susp and tabs
*dicloxacillin oral
*doxycycline 100 mg caps
*erythromycin oral suspension and tabs or caps
*erythromycin/sulfisoxazole susp
*griseofulvin 125 mg tabs
*isoniazid 300 mg tabs
*metronidazole 250 mg tabs
*nystatin oral suspension
*penicillin VK susp and 250 mg tabs
*rifampin 300 mg caps
*tetracycline 250 mg caps

Antibiotics-EENT
*Cortisporin® Otic Suspension
*gentamicin ophth. soln. 0.3%
*Neosporin® Ophth. Solution
*sulfacetamide ophth. oint. 10%

Antivirals
acyclovir 200 mg caps

Anthelmintics
mebendazole 100 mg chew tabs

Antiulcer Drugs
*amoxicillin oral
*bismuth subsalicylate 262 mg tabs
*metronidazole 250 mg tabs
*tetracycline 250 mg caps

GERD Agents
cisapride 20 mg tabs
omeprazole 20 mg caps

Other GI Agents
*dicyclomine tabs or caps
*Donnatal® tabs
*sulfasalazine 500 mg tabs

Anti-diarrheals
*loperamide 2 mg tabs or caps

Genitourinary Agents
*oxybutynin 5 mg tabs
*phenazopyridine 100 mg tabs

Gout Agents
*allopurinol tabs
*probenecid 500 mg tabs

Muscle Relaxants
*diazepam 5 mg tabs
*methocarbamol 500 mg tabs

Oral Corticosteroids
*prednisone 5 & 20 mg tabs
prednisone oral soln 5 mg/5 mL
prednisolone oral soln 15 mg/5 mL

Nasal Corticosteroids
*beclomethasone nasal inhaler

Asthma Agents
*albuterol oral inhaler
flunisolide oral inhaler
triamcinolone oral inhaler
*theophylline liquid 80 mg/15 mL
SloBid™ Gyrocaps 50, 200, 300 mg

Antihistamines / Decongestants
*Actifed® tabs
*chlorpheniramine 4 mg tabs
*chlorpheniramine syrup
*Dimetapp® Elixir
*Dimetapp® Extentabs
*diphenhydramine caps
*diphenhydramine syrup
*hydroxyzine syrup
*hydroxyzine tabs
*oxymetazoline nasal spray
*pseudoephedrine 30 mg tabs

Anticonvulsants
Dilantin® Infatabs 50 mg
Dilantin® Kapseals 100 mg
*phenobarbital elixir 20 mg/5 mL
*phenobarbital 30 mg tabs
*primidone 250 mg tabs
†Tegretol® 200 mg tabs

Anticoagulants
warfarin 5 mg tabs

Diuretics
*furosemide 40 mg tabs
*hydrochlorothiazide tabs
*Maxzide® tabs
*spironolactone 25 mg tabs

Vasodilators
*isosorbide dinitrate 10 mg tabs
nitroglycerin sublingual tabs

Lipid Lowering Agents
colestipol powder
*niacin tabs
pravastatin 10 mg, 20 mg, 40 mg tabs

Hypotensive / Cardiac Drugs
*atenolol tabs
*clonidine tabs
†Lanoxin® 0.25 mg tabs
lisinopril tabs
*propranolol 10 & 40 mg tabs
*quinidine gluconate 324 mg tabs
*quinidine sulfate tabs
terazosin tabs
*verapamil long-acting tabs

Diabetic Agents
*human insulin, regular & NPH

Electrolyte Replacement
*potassium chloride slow release tabs or caps

NSAIDS / Analgesics
*acetaminophen drops, elixir, and 325 mg tabs
*aspirin, enteric-coated 325 mg tabs
*ibuprofen susp and 400 mg tabs
*indomethacin 25 mg caps
*Tylenol #3® tabs

Migraine Agents
*Cafergot® tabs
*Fiorinal® tabs
*Midrin® caps

Attention Deficit / Narcolepsy Agents
*methylphenidate 10 mg tabs
*methylphenidate sustained release 20 mg tabs

Contraceptives
LoOvral®
*Norinyl 1+50®, Ortho-Novum 1/50®
*Ortho-Novum 1/35®, Norinyl 1+35®
Ortho-Novum 7/7/7®
Ovral®
Triphasil®/Tri-Levlen®

Estrogens / Progestins
conjugated estrogens 0.625 mg tabs
conjugated estrogen vaginal cream
*medroxyprogesterone 10 mg tabs

Thyroid / Antithyroid Agents
*propylthiouracil 50 mg tabs
†Synthroid® 100 mcg (0.1 mg) tabs

Topical Agents
*bacitracin ointment
*hydrocortisone 1% cream
Sebutone® shampoo
*Selsun® shampoo

Vitamins & Minerals
*ferrous sulfate concentrated soln. 125 mg/mL
*ferrous sulfate 325 mg tabs
*pyridoxine 50 mg tabs

Miotics
*pilocarpine ophth. solution

Miscellaneous
insect sting kit
InspirEase® spacer

generic products are available
†***DMSB sole source item***

Brand names are included for example only and are not meant to imply the recommendation of a specific product except for those products designated as sole source items by the Defense Medical Standardization Board.

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